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10/642,284	08/18/2003	Izumi Kumagai	4600-0106P	2450

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	02/07/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 02/07/2007.

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Office Action Summary	Application No.	Applicant(s)	
	10/642,284	KUMAGAI ET AL.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *14-22 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 23-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/03,3/05,7/05,9/06,1/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-13 and claims 23-27 to the extent claims 23-27 read on pharmaceutical compositions comprising a polypeptide product) in the reply filed on 8/14/2006 is acknowledged. The traversal is on the ground(s) that examining the polypeptide product along with the nucleic acid product would not be unduly burdensome for the examiner. This is not found persuasive because as explained in the restriction requirement mailed on 7/12/2006 the search for polynucleotides does not overlap with the search for the polypeptides. Furthermore, claims 23-27 are drawn to pharmaceutical compositions and pharmaceutical compositions comprising a polynucleotide product require consideration of different issues in examination of the claims than does examination of pharmaceutical compositions comprising polypeptide products. For example, the delivery considerations for polynucleotide pharmaceutical compositions are much different than for polypeptide pharmaceutical compositions.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-27 are pending. Claims 14-22, and 27,drawn to non-elected inventions, are withdrawn from consideration. Claims 1-13 and 23-26 (to the extent claims 23-26 comprise polypeptide products) are examined on the merits.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on Jan. 17, 2003. It is noted, however, that applicant has not filed a certified copy of the 2003-038643 Japanese application.

Claim Rejections - 35 USC § 112

4. Claims 1-13 and 23-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because of the phrase "a human epidermal growth factor (EGF) receptor". Does applicant mean a receptor from the human epidermal growth factor (EGF) receptor family? The confusion caused by the phrase is that "human epidermal growth factor (EGF) receptor" usually means the Her1 receptor.

Claim 13 is indefinite because of the phrase "a polypeptide constituting each region contained in the single-chain polypeptide". Does applicant intend to claim individual CDRs?

Claim 13 is also indefinite because of the phrase "two kinds of a single-chain polypeptide". It is not clear what is meant by "kind of single-chain polypeptide". This rejection would be obviated by amending claim 13 to delete the word "kind".

5. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the amendment to claims 9 and 10 introduces new matter into the specification as originally filed.

Claims 9 and 10 as originally filed referred to amino acid sequences of CDR1, CDR2 and CDR3 in the variable regions derived from a humanized anti-CD3 antibody OKT3 represented in Figure 21, as well as to amino acid sequences of CDR1, CDR2 and CDR3 in the variable regions derived from a humanized anti-human EGFR receptor antibody 528 represented in Figure 22. Examination of Figure 21 shows that both the heavy and light chain variable regions are depicted (for a total of 6 CDR regions). Examination of Figure 22 shows that both the heavy and light chain variable regions are depicted (for a total of 6 CDR regions). The amendment of claim 9, filed 11/13/2006, refers to only 3 CDR regions for OKT3 antibody (to be found in SEQ ID NO: 43), and only 3 CDR regions for the 528 antibody (to be found in SEQ ID NO: 44). Furthermore, the amendment filed 11/13/2006 indicates that the amino acid sequences for the CDRs of the 528 antibody correspond to regions of SEQ ID NO: 44. However, a comparison of SEQ ID NO: 44 with the amino acid sequence of Figure 22 shows that neither of the amino acid sequences of Figure 22 are the same as the amino acid sequence of SEQ ID NO: 44. Similarly, the amendment of claim 10, filed 11/13/2006, refers sequences having only 3 CDR regions for OKT3 antibody, and only 3 CDR regions for the 528 antibody, whereas the originally filed claims referred to Figures that presented 6 CDR regions each for antibodies OKT3 and 528. Furthermore, the amendment filed 11/13/2006 indicates that the amino acid sequences for the CDRs of the OKT3 antibody correspond to regions of SEQ ID NO: 45. However, a comparison of SEQ ID NO: 45 with the amino acid sequences of Figure 21 shows that neither of the amino

acid sequences of Figure 21 are the same as the amino acid sequence of SEQ ID NO: 45. Therefore, the amendment filed 11/13/2006 appears to have introduced new matter into the specification by one changing the scope of the claims and also by changing the structures of the CDRs encompassed by the claimed antibodies.

6. Claims 9, 10 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for humanized diabody-type bispecific antibodies that comprise all six CDRs of the two parent antibodies, does not reasonably provide enablement for humanized diabody-type bispecific antibodies that do not contain all six of CDRs of the parent antibodies, or contains CDRs that are altered from the CDRs of the parent antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Claims 9 and 10 are drawn to diabody-type bispecific antibodies that are humanized and have CDRs derived from a mouse antibody and other parts (framework regions) derived from a human antibody, wherein the diabody-type bispecific antibodies bind to a member of the epidermal growth factor receptor family, and to an antigen on a cell having phagocytosis or

cytotoxic activity, wherein the antibodies comprising at least one CDR selected from CDR sequences found in the amino acid sequence of SEQ ID NO: 43 and at least one CDR selected from CDR sequences found in the amino acid sequence of SEQ ID NO: 44. Thus, the claims read on humanized antibodies that do not contain all six CDRs of the parent antibody, or contain CDRs with alterations in the amino acid sequence. Claim 12 is drawn, in part, to a polypeptide constituting each region contained in a single-chain polypeptide. This appears to read on polypeptides that comprises regions such as CDR regions.

The specification teaches one example of a diabody-type bispecific antibody that binds to CD3 and also to EGFR (HER1). The parent antibodies are OKT3 and 528, which are both mouse antibodies and are known in the art (see Kipriyanov, G. et al., Protein Engineering, 10(4): 445-453, 1997, and US 4,943,533 (Mendelsohn)). The example provided by the specification is that of an antibody that has 6 CDR regions that, when associated together in the context of heavy and light chain to form a binding site, bind to CD3, and 6 CDR regions that when associated together in the context of heavy and light chains to form a binding site, bind to EGFR. In contrast, the claim 9 appears to be drawn to antibodies that comprise 2 CDRs that are from the OKT3 antibody, one CDR coming from the heavy chain and one CDR coming from the light chain. Claim 10 appears to be drawn to antibodies that comprise 6 CDRs that are from the 528 antibody. In both cases, the claims encompass antibodies that do not possess the full complement of CDRs. Additionally, because the claims do not recite the structures of all the CDRs from the parent antibodies, one interpretation of the claims is that they read on humanized diabody-type bispecific antibodies that possess CDRs that have been altered from the original sequences found in the parent antibody.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which heavy and light chain variable regions consists of three CDRs that provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity that is characteristic of a given antibody. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences, which maintain the required conformation of the CDRs, are required in order to produce a protein having antigen-binding function; and further, that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light chain variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff (Proc. Natl. Acad. Sci. USA, 79: 1979, 1982). Rudikoff teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the antibodies as defined by the claims, which may contain less that the full complement of CDRs from the heavy and light chain variable regions of the parent antibodies that bind CD3 and EGFR will have the required binding function of binding to both antigens, or in the case of claim 9, binding to any antigen. The claims as currently recited are drawn to humanized antibodies comprising less than the full complement of CDRs to form binding regions to bind to both antigens as required by the claims.

The specification provides no direction or guidance regarding how to produce the humanized antibodies as broadly defined by the claims, because the specification fails to teach how to make humanized antibodies that do not contain all of the CDRs present in the parent antibodies, or how to make humanized antibodies that contain altered CDRs. The relationship between structure and function in the protein and antibody arts is highly unpredictable. Therefore, one of skill in the art would have to engage in undue experimentation to practice the full scope of the claimed inventions. This experimentation would be undue experimentation because there is no guidance provided in the specification or in the prior art for producing useful antibodies that lack the full complement of CDRs from the parent antibody, and that also bind to CD3 and EGFR with sufficient affinity to operate in the claimed methods.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1, 2, 3, 5-8, 13, and 23-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Deo (US 5,922,845; issued July 13, 1999).

The claims are drawn to diabody-type bispecific antibodies having a first specificity to a human epidermal growth factor (EGF) receptor and a second specificity to a surface antigen expressed by a cell having phagocytosis or cytotoxic activity. The specification defines diabody-type bispecific antibodies as a small fragment of an antibody having two antigen-binding sites, where the fragment contains the variable region of the heavy chain (VH) and the variable region of the light chain (VL) in the same polypeptide chain, where, typically, the two domains in the same chain are linked together via linker that is too short to pair the above two domains, so that each domain will be paired with its complementary domain of another chain to form the two antigen-binding sites together (see specification page 6). The diabody-type bispcific antibody may be humanized, and the CDRs in the variable regions may be derived from a mouse antibody and the other parts of the variable regions derived from a human antibody. Claim 13 appears to be drawn to the individual single chain variable region fragments (scFv) that make up the diabody-type bispecific antibody, or to a polypeptide that comprises regions of the diabody-type bispecific antibody. Claims 23-26 are drawn to pharmaceutical compositions comprising the diabody-bispecific antibody of claim 1 or the polypeptides of claim 13. Claims 5 and 6 contain the recitations that the first and second specificities are "derived from" the variable regions in the heavy and light chains of antibodies 528 and OKT3, respectively. However, because the term "specificity" is interpreted to mean antigen binding region and because the phrase "derived from" is open to interpretation as to what parts and how much of the amino acid sequences of the named antibodies are included in the claimed bispecific antibodies, claims 5 and 6 are interpreted to be drawn to diabody-type bispecific antibodies that bind to EGFR and to a cell having phagocytosis or cytotoxic activity and that the antigen binding regions of the diabody-type

bispecific antibodies of claims 5 or 6 may have very little in common structurally (i.e. having as little as one amino acid in common) with either the 528 or the OKT3 antibodies.

Deo teaches bispecific antibodies having one binding specificity to the Fcα receptor, present on white blood cells (see column 1, lines 34-45). It appears that Fc receptors are found on some T cells (evidenced by Hoover, R.G. et al. J. Clin. Invest. 67: 308-311, 1981). The other specificity of the bispecific antibodies of Deo is to a tumor antigen, preferably an EGFR family receptor such as EGFR (see column 12, lines 38-56). Deo teaches that the bispecific antibodies may comprise at least two single chain molecules (see column 15, lines 9-27). Therefore, Deo teaches diabody-type bispecific antibodies having one specificity to an antigen expressed by a cell having phagocytosis or cytotoxic activity and another specificity to a human epidermal growth factor receptor. Deo teaches that the single chain molecules can be expressed separately (see column 15, lines 30-32). Therefore, Deo teaches individual single chain polypeptides that make up the diabody-type bispecfic antibodies. Deo also teaches humanized bispecific antibodies (see column 8, lines 33-45, column 8, line 66 – column 9, line 17). Deo teaches pharmaceutical compositions that comprise the bispecific antibodies (see column 15, line 58 to column 16, line 49). Therefore, Deo teaches the claimed inventions.

8. Claims 13 and 23-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Kipriyanov (Kipriyanov, G. et al., Protein Engineering, 10(4): 445-453, 1997).

Claim 13 appears to read on single chain Fv antibodies that bind to an antigen present on cytotoxic or phagocytic cells. Claims 23-26 is a pharmaceutical composition comprising the polypeptide of claim 13. The recitation of pharmaceutical composition and the intended uses of

the pharmaceutical compositions are intended uses that do not appear to affect the structure of the products contained within the composition.

Kipriyanov teaches a composition comprising an scFv in PBS, where the scFv comprises the heavy and light chain variable regions of the OKT3 antibody, which is an antibody that binds to CD3, a receptor on T cells (see page 446; see also 448, 2nd column). Therefore, Kipriyanov teaches a polypeptide and pharmaceutical compositions that are the same as that claimed.

9. Claims 1, 3-8, 12 and 23-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Carter (US 6,407,213; issued June. 18, 2002).

The claims are drawn to diabody-type bispecific antibodies having a first specificity that binds to a receptor of the EGFR family and a second specificity that binds to an antigen on a phagocytic or cytotoxic cell. In the broadest embodiment of a diabody-type bispecific antibody, the specification defines this phrase as a small fragment of an antibody having two antigen-binding sites. Therefore, the claims read on a bispecific $F(ab')_2$ fragment. The recitation of pharmaceutical composition and the intended uses of the pharmaceutical compositions are intended uses that do not appear to affect the structure of the products contained within the composition. Claims 5 and 6 contain the recitations that the first and second specificities are "derived from" the variable regions in the heavy and light chains of antibodies 528 and OKT3, respectively. However, because the term "specificity" is interpreted to mean antigen binding region and because the phrase "derived from" is open to interpretation as to what parts and how much of the amino acid sequences of the named antibodies are included in the claimed bispecific antibodies, claims 5 and 6 are interpreted to be drawn to diabody-type bispecific antibodies that

bind to EGFR and to a cell having phagocytosis or cytotoxic activity and that the antigen binding regions of the diabody-type bispecific antibodies of claims 5 or 6 may have very little in common structurally (i.e. having as little as one amino acid in common) with either the 528 or the OKT3 antibodies.

Carter teaches a humanized bispecific $F(ab')_2$ fragment, where one Fab' arm binds to CD3 and the other binds to $p185^{HER2}$ (Her2 or ErbB2; see column 56, line 60 – column 63, line 10). The humanized bispecfic $F(ab')_2$ comprises murine CDR sequences and human variable region sequences, with substitution of some human residues with murine residues (see column 60, lines 19-43). Carter teaches compositions for therapy (see column 45, line 41- column 46, line 2). Therefore, Carter teaches diabody-type bispecific antibodies and compositions that are the same as that claimed.

10. Claims 1-6 and 23-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Negri (Negri, D.R.M. et al. British Journal of Cancer, 72: 928-933, 1995; cited in the IDS).

The claims are drawn to diabody-type bispecific antibodies having a first specificity that binds to a receptor of the EGFR family and a second specificity that binds to an antigen on a phagocytic or cytotoxic cell. In the broadest embodiment of a diabody-type bispecific antibody, the specification defines this phrase as a small fragment of an antibody having two antigen-binding sites. Therefore, the claims read on a bispecific $F(ab')_2$ fragment. The recitation of pharmaceutical composition and the intended uses of the pharmaceutical compositions are intended uses that do not appear to affect the structure of the products contained within the composition. Claims 5 and 6 contain the recitations that the first and second specificities are

"derived from" the variable regions in the heavy and light chains of antibodies 528 and OKT3, respectively. However, because the term "specificity" is interpreted to mean antigen binding region and because the phrase "derived from" is open to interpretation as to what parts and how much of the amino acid sequences of the named antibodies are included in the claimed bispecific antibodies, claims 5 and 6 are interpreted to be drawn to diabody-type bispecific antibodies that bind to EGFR and to a cell having phagocytosis or cytotoxic activity and that the antigen binding regions of the diabody-type bispecific antibodies of claims 5 or 6 may have very little in common structurally (i.e. having as little as one amino acid in common) with either the 528 or the OKT3 antibodies.

Negri teaches a bispecific $F(ab')_2$ fragment, where one Fab' arm binds to CD3 and the other binds to EGFR (Her1; see abstract and page 929, 1st column). Negri teaches injecting mice with the bispecific $F(ab')_2$ fragment (page 929, 2nd column). Therefore, Negri teaches diabody-type bispecific antibodies and compositions that are the same as that claimed.

11. Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by Clackson (Clackson, T. et al. Nature, 352: 624-628, 1991).

Claim 13 is drawn to polypeptides constituting regions contained in a single-chain polypeptide. Claim 13 fails to recite any binding activity for the claimed polypeptides, and it appears to be drawn to polypeptides that comprise regions of single-chain polypeptides, such as CDR regions.

Clackson teaches V_H and V_κ sequences, some of which comprise CDR regions that are the same as CDR regions found in SEQ ID NO: 44, for example (see page 626, V_κ sequence "f";

and sequence alignment. Therefore, Clackson teaches polypeptides that are the same as that claimed.

12. Claims 1-13 and 23-26 are rejected under 35 U.S.C. 102(a) as being anticipated by either Abstract #2125 (Abstract #3P-214, 61st Annual Meeting of the Japanese Cancer Association, August 20, 2002; cited in the IDS) or Abstract #3P-214 (Abstract #2125, 75th Annual Congress of The Japanese Biochemical Society, 74(8): August 25, 2002; cited in the IDS).

Both references are in Japanese. However, applicants have provided a summary in the English language, which states that both abstracts describe an outline of the production of the bispecific antibody of the present invention, where the bispecific antibody comprises binding sites from the OKT3 and the 528 antibodies. The inventorship of each abstract appears to be different from that of the instant invention, because for abstract #2125 there are 12 inventors, whereas for abstract #3P-214 there are 5 authors. The instant application names 4 inventors. Therefore, either of abstract 2125 or abstract #3P-214 teaches the diabody-type bispecific antibodies and pharmaceutical compositions that are the same as that claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-8, 12 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Renard (Renard, I., et al. American Journal of Pathology, 160(1): 113-122, 2002, Jan.) in view of Krebber (Krebber, A. et al. Journal of Immunological Methods, 201: 35-55, 1997) and further in view of Gussow and Seemann (Gussow, D. and Seemann, G. Methods in Enzymology, 203: 99-121, 1991).

Renard teaches an anti-CD3/anti-EGFR bispecific antibody comprising the monoclonal antibody 298.1 (mouse IgG2a) that recognizes CD3 and comprising the monoclonal antibody MINT5 (mouse IgG1) that recognizes EGFR. Renard suggests, but does not teach, that the

bispecific anti-CD3/anti-EGFR antibody may be used in methods of tumor therapy, and that efficacy may be improved if the bispecific antibody were expressed as single-chain bispecifics, bispecific diabodies or bispecific minibodies made from humanized or fully human antibodies.

Krebber teaches methods for cloning functional antibody variable domains from hybridomas for the purpose of expressing scFvs (see abstract and pages 37-41). Gussow and Seeman teach methods for humanizing antibodies (see entire document) and teach that framework substitutions may have to be made (see page 112). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Krebber and of Gussow and Seemann to make humanized, bispecific diabody-type antibodies that comprised an anti-CD3 binding site and an anti-EGFR binding site. One would have been motivated to have modified the bispecific antibody of Renard to produce a bispecific based on a fragment such as scFv and to humanize the bispecific because Renard suggests that such modifications will improve the efficacy of the bispecific antibody in methods of treatment. One of ordinary skill in the art would have had a reasonable expectation of success in making a diabody-type bispecific antibody from the bispecific antibody of Renard because the methods are well known in the art for making antibody fragments and for humanization of the fragments, as evidenced by the teachings of Krebber and of Gussow and Seemann.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
January 30, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER